

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY



(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 22 SEP 2006

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Applicant's or agent's file reference WJW/FP6384713	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/US2005/041726	International filing date (day/month/year) 17.11.2005	Priority date (day/month/year) 19.11.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D231/16 C07D231/12 C07D403/12 C07D487/08 C07D401/12 C07D405/12 C07D409/12 C07D413/12 C07D417/12 A61P29/00 A61K31/4155		
Applicant ARENA PHARMACEUTICALS, INC. et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 21 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 04.07.2006	Date of completion of this report 21.09.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Härtinger, Stefan Telephone No. +49 89 2399-8289 	

**INTERNATIONAL PRELIMINARY REPORT
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-172 as originally filed

Claims, Numbers

1-76 received on 26.07.2006 with letter of 25.07.2006

Drawings, Sheets

1-12 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 38-49

because:

- ☒ the said international application, or the said claims Nos. 38-49 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-76
	No: Claims	
Inventive step (IS)	Yes: Claims	1-76
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-37,50-76
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Re Section I:

1. The set of claims filed with the letter of 25.7.06 appears to meet the requirements of Art. 34(2)(b) PCT because the amendments do not go beyond the disclosure in the international application as originally filed.

New claim 1 is derived from a combination of previous claims 1 and 3 (i.e. V is O) with the additional introduction of a disclaimer directed to the family of oxiranyl compounds disclosed in D1. It is noted that said oxiranyl compounds of formula II or III have been disclosed exclusively in the context of synthetic intermediates (see column 3, lines 49-60). As such, the disclaimer removes the overlap with D1 of accidentally disclosed compounds which are devoid of pharmaceutical activity.

All further amendments relate to the renumbering of previous claims and the adjustment of their dependencies.

Re Section III:

1. Claims 38-49 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Section V:

1. The application relates basically to 5-HT_{2A} antagonists based on pyrazol-3-yl-aniline derivatives having an oxygen linked substituent at position 4. The relevant prior art has been cited in the search report.

D1: US-A-4 409 231 (STENZEL ET AL) 11 October 1983 (1983-10-11)

D2: WO 98/24785 A (FUJISAWA PHARMACEUTICAL CO., LTD; ITO, KIYOTAKA; SPEARS, GLEN, W; YAMA) 11 June 1998 (1998-06-11)

D3: WO 2004/058722 A (ARENA PHARM INC [US]; TEEGARDEN BRADLEY [US]; JAYAKUMAR HONNAPPA [US];) 15 July 2004 (2004-07-15)

D4: WO 03/062206 A (ARENA PHARMACEUTICALS, INC; TEEGARDEN, BRADLEY; DROUET, KEITH; JAYAKUM) 31 July 2003 (2003-07-31)

2. The claimed matter appears to be novel in the sense of Art. 33(2) PCT. The novel technical element of the present compounds as defined in claim 1 resides from the substituent "-V-W-R4", requiring that a cyclic residue containing a heteroatom (R4) is bonded via an optional linker (W) and an oxygen atom (V) to the benzene ring. No such structural element is disclosed for the compounds disclosed in D2-D4. Due to the disclaimer at the end of claim 1, the overlap with families of oxiranyl intermediate compounds disclosed in D1 have been excluded (see Section I above).
3. D1 discloses compounds that are anti-hypertensive agents. D2-D4 teaches compounds which are active at the family of 5-HT receptors. As such the present compounds share the utility with that of the mentioned prior art. The structural difference to the afore mentioned prior art is the substituent "-V-W-R4", wherein V is an oxygen atom and R4 is heterocyclic ring structure.

The technical problem is regarded to be the provision of further 5-HT_{2A} receptor active compounds with utility in the treatment of diverse pathologies, such as hypertension, platelet aggregation, inflammation, behavioural diseases, etc. In the light of the binding assays disclosed on page 164 of the description, the problem has been solved.

The solution appears to have involved an inventive step, because the introduction of an oxygen linked fragment "-V-W-R4" in alpha position to the pyrazole moiety has nowhere suggested in the prior art, and there is no prior art teaching that the said oxygen linked fragment would be equivalent to those residues present in the said alpha position of prior art compounds.

The claimed subject-matter therefore appears to have met the requirements of Art. 33(3) PCT.

Re Section VI:

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1. The international patent applications D5 (= WO 2005/103011 A, ARENA PHARMACEUTICALS, INC; FRITCH, JOHN ROBERT; CARLETON, FIONA M; LA, 2005-11-03) and D6 (= WO 2005/012254 A, ARENA PHARMACEUTICALS, INC; TEEGARDEN, BRADLEY; JAYAKUMAR, HONNAPPA; L, 2005-02-10) have been published between one of the present priorities and the filing date of the present application. The 5-HT_{2A} antagonists disclosed therein do therefore not belong to the state of the art as defined in the PCT. By consequence, D5 and D6 have been disregarded from further consideration.

Re Section VIII:

1. The passages on page 102 (lines 23-35) and page 172 (last paragraph) lead to doubts as to the exact subject-matter for which protection is sought. As such, the claims are rendered unclear.